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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/696,791	10/25/2000	Joan M. Robbins	480124.407	4714

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EXAMINER
LACOURCIERE, KAREN A

ART UNIT	PAPER NUMBER
1635	15

DATE MAILED: 07/09/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

FILE COPY

Office Action Summary	Application No.	Applicant(s)	
	09/696,791	ROBBINS ET AL.	
	Examiner	Art Unit	
	Karen A. Lacourciere	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)[·] Responsive to communication(s) filed on *08 April 2003* .

2a)[ ] This action is **FINAL**. 2b)[X] This action is non-final.

3)[ ] Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)[·] Claim(s) *71-79 and 85-110* is/are pending in the application.

4a) Of the above claim(s) *79 and 109* is/are withdrawn from consideration.

5)[ ] Claim(s) _____ is/are allowed.

6)[·] Claim(s) *71-78, 85-108 and 110* is/are rejected.

7)[ ] Claim(s) _____ is/are objected to.

8)[ ] Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)[ ] The specification is objected to by the Examiner.

10)[ ] The drawing(s) filed on _____ is/are: a)[ ] accepted or b)[ ] objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)[ ] The proposed drawing correction filed on _____ is: a)[ ] approved b)[ ] disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)[ ] The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)[ ] Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)[ ] All b)[ ] Some * c)[ ] None of:

1.[ ] Certified copies of the priority documents have been received.

2.[ ] Certified copies of the priority documents have been received in Application No. _____ .

3.[ ] Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)[ ] Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) [ ] The translation of the foreign language provisional application has been received.

15)[ ] Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) [ ] Notice of References Cited (PTO-892)
2) [ ] Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) [ ] Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) [ ] Interview Summary (PTO-413) Paper No(s). _____ .
5) [ ] Notice of Informal Patent Application (PTO-152)
6) [ ] Other: .

DETAILED ACTION

Election/Restrictions

This application contains claims 79 and 109 drawn to an invention nonelected with traverse in Paper No. 10. A complete reply to the final rejection must include cancelation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claim Objections

Claim 103 objected to under 37 CFR 1.75 as being a substantial duplicate of claim 102. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claim Rejections - 35 USC § 112

The rejection of record of claims 85, 86, 107 and 108 under 35 USC 112, second paragraph, set forth in the prior Office action, mailed 11-06-2002, is withdrawn in response to Applicant's amendments filed April 8, 2003.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 71-78 and 85-108 are maintained as rejected and claim 110 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating proliferative vitreoretinopathy (PVR) by intravitreally injecting a ribozyme consisting of SEQ ID NO: 4385, for reducing post-trabeculectomy hyper-proliferation in the eye using an intraocularly administered ribozyme consisting of SEQ ID NO:4385 and inhibiting scar formation on the skin of the eye using a locally administered ribozyme consisting of SEQ ID NO:4385, does not reasonably provide enablement for treating generally any proliferative eye disease by locally administering a ribozyme targeted to a PCNA encoding nucleic acid comprising SEQ ID NO: 4145, or for treating a proliferative eye disease by locally adminstering a vector expressing a ribozyme, or treating PVR, reducing post-trabeculectomy hyper-proliferation or reducing scar formation on the skin of the eye using any ribozyme other than SEQ ID NO: 4385. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The following factors have been considered in formulating this rejection (*In re Wands*, 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988)): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

Claims 71-78, 85-108 and 110 are drawn broadly, and would encompass methods of treatment for a broad class of eye disorders with a broad range of underlying biological cause. For example, the claims include particular limitations wherein the disorder is various forms of retinopathy, diabetic, vitreoretinopathy, sickle cell retinopathy and retinopathy of prematurity, however, the broad term "proliferative eye disorder" would include disorders like scarring on the eyelid and melanoma on the eyelid. Additionally, the methods claimed would broadly encompass using any ribozyme targeted to a nucleic acid comprising SEQ ID NO:4145 encoding PCNA, including a ribozyme targeted to an entirely different region of a nucleic acid comprising SEQ ID NO:4145 encoding PCNA than the region targeted by the exemplified embodiments.

The specification provides one example, wherein a dispase induced rabbit model of PVR is treated using an intravitreally injected ribozyme consisting of SEQ ID NO: 4385 or 4383 (example 8). In the one example provided, SEQ ID NO 4385 results in a significant improvement for PVR (see Table 23), however, SEQ ID NO: 4383 does not appear to provide the same treatment effect (for example, SEQ ID NO:4383, PN30004, has an average score of 3.1±1.3, a range of 1.8 to 4.4, and controls are ranges of 3.5 to 6.5, or even as low as 2.5±0.7, 2.2±0.4). SEQ ID NO:4383, for example, appears to provide an effect that is comparable to that of the control and, therefore, does not seem to provide a treatment. Additionally, the specification provides an example of treating scarring using SEQ ID NO:4383 applied topically and the declaration filed April 8, 2003 provides an example of reducing post-trabeculectomy hyper-proliferation using a locally

administered ribozyme consisting of SEQ ID NO:4383. The specification does not provide any examples or guidance on treating any disorder encompassed in the claims besides PVR, post-trabeculectomy hyper-proliferation and eye-lid scarring in vivo, nor does it provide any guidance on in vivo treatment using any other ribozyme targeted to a nucleic acid comprising SEQ ID NO: 4145 encoding PCNA , nor does it provide any guidance on methods of treatment using a ribozyme delivered locally to the eye using a vector.

At the time the instant invention was made, the therapeutic use of oligonucleotides, including ribozymes, and gene therapy methods (eg. vector expressed ribozymes) was a highly unpredictable art due to obstacles that continue to hinder the therapeutic application of oligonucleotides *in vivo* (whole organism) (see for example Agrawal et al. (Molecular Medicine Today, Vol 6, p 72-81, February 2000), Branch (TIBS 23, Feb 1998, p45-50), Green et al. (J. Am Coll. Surg., Vol 191, No. 1, July 2000, p 93-105), Jen et al. (Stem Cells 2000, Vol. 18, p 307-319)). Theses references are directed mainly to antisense considerations, however, these obstacles would also apply to ribozymes. Such obstacles include, for example, problems with delivery, target accessibility and the potential for unpredictable, non-specific effects. Jen et al. state (see page 313, second column, second paragraph) "One of the major limitations for the therapeutic use of AS-ODNs and ribozymes is the problem of delivery....Presently, some success has been achieved in tissue culture, but efficient delivery for *in vivo* animal studies remains questionable". Jen et al. outlines many of the factors limiting the application of oligonucleotides for in vivo therapeutic purposes and concludes (see p

315, second column), "Given the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has proven elusive."

Green et al. state, "It is clear that the evolution of antisense technology from a laboratory research tool into a mechanism for designing active and effective drugs is far from complete. Although there is little doubt that systemically administered antisense ODNs can inhibit the expression of specific genes in patients, the effectiveness of such therapy in modifying the course of a particular illness has not yet been established....Clearly, additional work must be done to unravel the complex problems associated with drug delivery, mRNA targeting and aptameric, nonantisense effects."

Given this unpredictability, the skilled artisan would require specific guidance to practice the claimed methods *in vivo*, with a resultant therapeutic outcome, as claimed. The specification provides examples wherein one ribozyme is effective when provided by local administration, however, this example does not provide guidance for generally any ribozyme, due to differences in metabolites and clearance rates, local concentration, differences in target site accessibility, cellular uptake differences and the potential for non-specific effects. For example, on page 29 of the specification, the specification demonstrates how several ribozymes have very different half-lives in serum and in cell lysate, due to only small differences in modifications of each ribozyme. This difference in half-life would have a large impact on the efficacy of a ribozyme in vivo. Additionally, difference in sequence and modification would cause each ribozyme to have a varying binding rate to the target molecule, and a different cellular uptake, which would have a large impact on in vivo efficacy. For example,

Agrawal et al. (see p 79-80, section entitled *Cellular uptake facilitators for in vitro studies*) states "The cellular uptake of negatively charged oligonucleotides is one of the important factors in determining the efficacy of antisense oligonucleotides.....In vitro, cellular uptake of antisense oligonucleotides depends on many factors, including cell type, kinetics of uptake, tissue culture conditions, and chemical nature, length and sequence of the oligonucleotide. Any one of these factors can influence the biological activity of an antisense oligonucleotide." Due to differences in the uptake and binding activity for an individual ribozyme, the efficacy observed for SEQ ID NO: 4385 would not predictably translate to *in vivo* results for any other ribozyme, as supported by the large difference seen between SEQ ID NO:4383 and 4385.

Additionally, the claimed methods are drawn to methods wherein a vector expressing a ribozyme is used in the claimed methods of treatment, which would encompass gene therapy methods. The specification does not disclose any methods wherein an expressed ribozyme is used to treat a proliferative eye disease. At the time of the instant invention and even to date, gene therapy methods were highly unpredictable (see, for example, Verma et al. or Anderson, W.F.), and had many of the same problems as discussed for antisense and ribozymes. Gene therapy methods have additional considerations, for example, vectors can result in unpredictable immune responses that preclude a therapeutic effect and often vectors do not provide a sustained expression level, and expression requires a vector particularly designed for a given cell, for example, vectors require an appropriate enhancer-promoter combination, the determination of which is trial and error for a given cell type (see for example,

Verma et al.) The specification provides no guidance on how to practice the claimed methods wherein a vector expressing a ribozyme is used to treat a proliferative eye disease, for example, there is no guidance on how to provide sufficient sustained expression in the target tissue of the eye to provide a therapeutic effect, what type of vector to use, for example, what type of promoter-enhancer combination would provide an effective expression level. The field of gene therapy does not have specific guidelines by which one skilled in the art can practice the claimed gene therapy methods successfully, nor is this guidance provided in the specification. Therefore, the skilled artisan would need to determine this de novo, through undue trial and error experimentation.

The claimed methods additionally encompass methods wherein a decoy oligonucleotide is delivered in addition to a ribozyme to treat a proliferative eye disease. Dzau (Dzau, V. (Circ. Res. 2002; 90:1234-1236.)) discusses the difficulty of using decoy oligonucleotides "The long term success of TFD oligonucleotide as a broadly utilized therapeutic modality will depend on several critical factors. These include the specificity of the TFD, the stability of the oligonucleotide, and the efficiency of tissue/cellular delivery...Another major determinant of TFD effect is the efficiency of cellular uptake and delivery...Finally the timing of treatment with TFD may also be important in influencing the therapeutic effect." (see Dzau, p 1235, first column). As Dzau points out, various strategies employed to overcome these hurdles have met with varied success. The specification has not provided any specific decoy oligonucleotides that are effective to treat a proliferative eye disease, nor has the specification provided any examples or

specific guidance by which the skilled artisan would be able to treat the broad range of proliferative eye diseases encompassed in the claims, for example, temporal considerations for the administration of a decoy oligonucleotide, nor does the field provide such specific guidelines.

Therefore, to practice the claimed methods of treatment for a proliferative eye disease it would require the skilled artisan to undergo undue trial and error experimentation to practice the claimed methods over the full scope claimed.

Response to Amendment

The Declaration under 37 CFR 1.132 filed April 8, 2003 is insufficient to overcome the rejection of claims 71-78 and 85-108 based upon a lack of an enabling disclosure as set forth in the last Office action because: The Declaration does not address the scope of the claimed methods of treatment. The declaration provides evidence related to one further method of treatment, however, the claims are directed to a much larger scope, encompassing treatments for a broad genus of conditions. Further, it provides evidence for only one ribozyme (SEQ ID NO:4385), but the claims are directed to a broad genus of ribozymes. The declaration provides evidence of a vector expressed ribozyme, however, the tissues used in the example are smooth muscle cells and are not relevant to the claimed methods, which require expression of a vector in cells and tissues of the eye. The declaration demonstrates 6 active ribozymes in vitro, however, this does not address the claimed methods, which are drawn to treatment methods in vivo. The field of ribozyme treatment indicates that there is no

predictable direct correlation between in vitro cleavage and in vivo treatments. Further, the exemplified ribozymes are not directed to the mRNA targeted in the claimed methods. The claimed methods are directed to PCNA ribozyme treatments whereas the declaration demonstrates 6 ribozymes targeted to IL-1 beta and are not relevant to the claimed methods.

Response to Arguments

Applicants arguments filed April 8, 2003 have been fully considered, however, they are not found to be persuasive because the arguments do not address the scope of the claimed methods.

In response to the rejection of record of claims 71-78 and 85-108 under 35 USC 112, first paragraph, set forth in the prior Office action, Applicant argues that the Declaration filed April 8, 2003 provides an example of reducing post-trabeculectomy hyper-proliferation in an in vivo eye model using a locally administered ribozyme, that the specification provides an example of treating scarring using a locally administered ribozyme. Applicant argues that the three conditions exemplified, PVR, scarring and post-trabeculectomy hyper-proliferation are associated only by the fact that they are proliferative diseases involving a cyclin PCNA and therefore, the specification is enabled to treat any proliferative eye disease involving a PCNA, including any proliferative eye disease. This is not found to be persuasive because the arguments and declarative evidence do not address the broad scope of the claimed methods. Applicant does not provide any evidence to support the assertion that the only linking

factor in these conditions is a cyclin PCNA, or that the results shown with these conditions correlates with all proliferative eye diseases and all PCNA targeted ribozymes. For example, whether inhibition of expression of a PCNA even results in a treatment effect for the very broad scope of conditions encompassed in the term "proliferative eye disease" and whether other ribozymes targeted to a PCNA mRNA are effective in vivo to provide a treatment effect. Given, for example, the large difference in activity of ribozymes, the potential for non-specific effects (e.g. that the results observed for SEQ ID NO:4383 are due to unpredictable non-specific effects) and the unpredictability of target site accessibility in vivo, it is unpredictable that the results observed for one ribozyme would correlate with treatment effects for generally any ribozyme.

Applicant argues that the scope of "proliferative eye disease" does not encompass disorders such as eyelid scarring or melanoma on the eyelid because these disorders are skin disorders. This is not found to be persuasive because the term "proliferative eye disease" is broad and has not been defined to exclude a wide range of conditions, including for example, eyelid scarring and melanoma of the eyelid. Although these disorders may also be defined as "skin disorders" it does not preclude these disorders as also falling within the scope of a "proliferative eye disease".

Applicant argues that the Declaration filed April 8, 2003 provides data that demonstrates an AAV vector adapted to express a PCNA ribozyme of the invention in smooth muscle cells and effectively inhibiting cell proliferation, which enables the vector delivery of the ribozymes of the invention. This is not found to be persuasive because

this example is not relevant to the claimed methods because it does not address cells and tissues associated with the claimed methods of treatment. As discussed in the rejection of record, a vector and promoter and enhancer sequences are highly cell type dependent and determining a vector for gene therapy for a particular cell or tissue type is unpredictable and requires empirical determination. A vector that expresses a ribozyme in smooth muscle cells in vitro would not predictably express a ribozyme at a concentration and for a duration sufficient to provide a therapeutic effect in cells and tissues involved in the broad range of proliferative eye diseases encompassed in the claims.

Applicant argues that in Table 23 of the specification the data demonstrates both SEQ ID NO:4385 and 4383 provided significant improvement in treating PVR and that SEQ ID NO:4383 does not need to be as effective as SEQ ID NO:4385, but rather merely needs to demonstrate an effect. Applicant argues this demonstrates any PCNA targeted ribozyme will be effective in treating a proliferative eye disease. This is not found to be persuasive because in examination of Table 23 it appears that when considering the margin of error in the experiments SEQ ID NO:4383 does not actually provide a better effect than the control.. Further, both SEQ ID NO:4385 and 4383 showed cleavage activity in an in vitro assay, however, in vivo SEQ ID NO:4385 and 4383 behave very differently with respect to treatment effects. This supports the rejection of record in that it demonstrates that there is not a direct and predictable correlation between in vitro cleavage activity for a ribozyme and an in vivo treatment effect.

Applicant argues that the rejection of record depends on the assertion that ribozyme therapy is unpredictable and that the rejection analogizes ribozymes to antisense technology, however, ribozymes are more predictable than antisense. Applicant argues that finding an active ribozyme is far more predictable than finding an active antisense molecule because the number of possible ribozymes targeted to a sequence is smaller and provides references to support that determining an active ribozyme is routine and provides data in the declaration filed April 8, 2003 that demonstrates 6 active ribozymes for IL-1 beta mRNA. These arguments are not found to be persuasive because the issue is not whether a ribozyme can be designed that cleaves an mRNA in vitro. The issue is whether the ribozymes encompassed in the claimed methods of treatment can be provided to a target cell in the eye such that the target PCNA mRNA is cleaved in vivo and at a concentration sufficient to inhibit the expression of the target PCNA mRNA to a level that will provide a treatment effect for a very broad genus of conditions, the full scope of which are not even clearly associated with PCNA. The field of ribozymes indicates that treatment effects in vivo are unpredictable. The references cited indicate that ribozyme therapies are unpredictable and ribozyme treatments experience the same unpredictability issues as antisense treatments (see for example Jen et al.) for similar reasons. Further, the examples of IL-1 beta ribozymes are not even targeted to PCNA mRNA, as required by the claimed methods.

Applicant argues the ribozymes of the invention have been shown to be active in vivo and therefore the claims are enabled. This argument is not found to be persuasive

because only one species of ribozyme encompassed in the genus of ribozymes used in the claimed methods has been shown to be effective in vivo (SEQ ID NO:4385) and that one ribozyme has only been shown to be effective in three conditions encompassed within the broad genus of treatment methods claimed. This does not address the scope of the claimed methods of treatment.

Conclusion

Any rejection of record not repeated herein is considered to be withdrawn.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Lacourciere whose telephone number is (703) 308-7523. The examiner can normally be reached on Monday-Thursday 8:30-6:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on (703) 308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 305-1935 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Karen A. Lacourciere

June 28, 2003

KAREN LACOURCIERE
PATENT EXAMINER